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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

ATTACHMENT TO ADVISORY ACTION

Applicants' After-final Amendment

1) Acknowledgment is made of Applicants' after-final amendment filed 04/11/08 in response to the final Office Action mailed 02/11/08. The after-final amendment has been entered.

Status of Claims

2) No claims have been amended.

Claims 1-7 and 9-17 are pending and are under examination.

Terminal Disclaimers

3) Acknowledgment is made of Applicants' terminal disclaimers filed 02/11/08 disclaiming the terminal portion of any patent granted on this application, which would extend beyond any patent granted on the co-pending applications, 09/445,517 and 10/851,574.

Prior Citation of Title 35 Sections

4) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

5) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Objection(s) Withdrawn

6) The objection to the specification made in paragraph 10(a) of the Office Action mailed 06/01/06 and maintained in paragraph 8 of the Office Action mailed 04/23/07 and paragraph 6 of the Office Action mailed 02/11/08 is withdrawn in light of Applicants' amendment to the specification.

Rejection(s) Withdrawn

7) The provisional rejection of claims 1-6 made in paragraph 10 of the Office Action mailed 11/13/00 under the judicially created doctrine of double patenting over the claims of the pending application, SN 09/445,517, and maintained in paragraph 9 of the Office Action mailed 05/30/02, paragraph 27 of the Office Action mailed 06/01/06, and paragraph 16 of the Office Action mailed 04/23/07, and paragraph 7 of the Office Action mailed 02/11/08 is withdrawn in light of Applicants' terminal disclaimer disclaiming the terminal portion of any patent granted on this application which would extend beyond any patent granted on the co-pending application, 09/445,517.

8) The provisional rejection of claims 7, 13, 14 and 16 made in paragraph 37 of the Office Action mailed 06/01/06 and maintained in paragraph 17 of the Office Action mailed 04/23/07 and paragraph 8 of the Office Action mailed 02/11/08 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 33 of the co-pending application 09/445,517, is withdrawn in light of Applicants' terminal disclaimer disclaiming the terminal portion of any patent granted on this application which would extend beyond any patent granted on the co-pending application, 09/445,517.

9) The provisional rejection of claims 7, 14 and 16 made in paragraph 38 of the Office Action mailed 06/01/06 and maintained in paragraph 18 of the Office Action mailed 04/23/07 and paragraph 9 of the Office Action mailed 02/11/08 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 6 of the co-pending application, 10/851,574, is withdrawn in light of Applicants' terminal disclaimer disclaiming the terminal portion of any patent granted on this application which would extend beyond any patent granted on the co-pending application, 10/851,574.

10) The rejection of claims 16 and 17 made in paragraph 31 of the Office Action mailed 2/11/08 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn upon further consideration.

Rejection(s) Maintained

11) The rejection of claims 7, 14, 16 and 17 made in paragraph 26 of the Office Action mailed 02/11/08 under the judicially created doctrine of obviousness-type double patenting

as being unpatentable over claims 34 and 35 of the US patent 5,686,411 issued to Gaeta *et al*. ('411, already of record) as evidenced by Tsanev (*Vutr. Boles* 23: 12-17, 1984, abstract), is maintained for the reasons set forth therein and herein below.

Applicants submit the following arguments:

(a) The cited claims of the '411 patent are silent with regard to treating obesity. (b) Nothing in the cited claims teaches or suggests the identification of or intent to treat a subject in need of treatment for obesity. (c) Even if obesity is common among those with diabetes as asserted by the Tsanev reference, a claim to treating diabetes mellitus with an amylin agonist analogue does not teach or suggest treating obese patients as claimed. (d) The courts have held that the phrase 'in need thereof' is meaningful and that the claims' recitation of a patient or a human 'in need' gives life and meaning to the preambles' statement of purpose. (e) Applicants cite case law and assert that anticipation based on inherency is appropriate only when the prior art relied upon necessarily includes all of the elements of the claims in question and is the natural result of following the instructions or examples of the prior art. To demonstrate inherency, it was necessary to show that the prior art necessarily, always functions in accordance with the claims addressed. (f) The requirement that the teaching of a reference always, under any circumstances, necessarily satisfies the recitation of the claims to make out a case of inherent anticipation was reaffirmed by the Federal Circuit in *Abbott Laboratories v. Baxter Pharmaceutical Products*, *Inc*., 471 F.3d 1363, 1368 (Fed. Cir. 2006). (g) It is well settled that a determination of inherency cannot be established by probabilities or possibilities, but that it is incumbent upon the Office to establish the inevitability of the inherency which is propounded. (h) Tsanev's disclosure that 80-90% of diabetic patients are obese falls short of the 100% (i.e., always, under any circumstances) criterion required by the present claims and required by the law.

Applicants' arguments have been carefully considered, but are not persuasive. Contrary to Applicants' assertion, the prior art method necessarily includes all of the elements of the instant claims. As set forth previously, the '411 patent's patient seen by a medical practitioner, i.e., a human having diabetes mellitus, was administered with a therapeutically effective amount of the amylin agonist of claim 19, ^{25,28,29}Pro-human

amylin (SEQ ID NO: 1 or pramlintide), the same amylin agonist analogue recited in instant claim 3. The method of treatment claimed in claims 34 and 35 of the '411 patent includes administering to such a patient with diabetes mellitus a therapeutically effective amount of the amylin agonist of claim 19, ^{25,28,29}Pro-human amylin (SEQ ID NO: 1 or pramlintide). The portion of the disclosure of the '411 patent at second paragraph under 'Summary of the Invention' supporting the limitations 'diabetes mellitus' and 'administration of …. an amylin agonist analogue' include insulin-requiring diabetes mellitus and administration of an amylin agonist analogue alone (i.e., consisting of) or in conjunction with (comprising or consisting essentially of) insulin or a glucagon, i.e., not in conjunction with another obesity relief agent. The portion of the disclosure of the '411 patent at lines 53-59 in column 8 supporting the limitation 'therapeutically effective amount' of the amylin agonist includes the dosage units of 0.1 to 5 mg or 0.5 to 1.0 mg of the amylin agonist. The amount effective to inhibit weight gain or induce weight loss, i.e., treat obesity, encompassed in the instant claims as described in the instant application of about 0.01 milligrams to about 5 milligrams per day, about 0.05 milligrams to about 2 milligrams per day, about 0.1 milligrams to about 1 milligram per day, or 300 micrograms per dose, falls within the range disclosed in the '411 patent. Given the art-known prevalence of intrinsic obesity in as many as 80% to 90% of diabetic patients as disclosed by Tsanev, 80-90% of the human diabetic patients used in the method disclosed in the '411 patent qualified as human patients in need of treatment for obesity. Therefore, the method of the '411 patent comprising or consisting of the administration of 0.1 to 5 mg, or 0.5 to 1.0 mg of the amylin agonist, ^{25,28,29}Pro-human amylin alone or in conjunction with insulin or glucagon, to 80-90% of the human diabetic patients anticipates the instant claims. Given that the method step of the '411 patent and the instant claims are the same, the amylin agonist analogue pramlintide used and its amount administered are the same, and the human diabetic patients used are the same (80-90% of whom are known to be obese), the method of the '411 patent is expected to bring about a weight gain-inhibiting effect, weight loss-inducing effect, or obesity-treating effect in the intrinsically obese diabetic patient administered with a therapeutically effective amount of the pramlintide as claimed in the instant invention. Since the structural limitations of the instantly claimed method and *all* of

the criteria required by the instant claims are met by the disclosure of Gaeta *et al*. ('411), Gaeta's ('411) method is expected to serve necessarily as the instantly claimed method and is expected to bring about the weight gain inhibiting effect, weight loss-inducing effect, or obesity-treating effect.

Contrary to Applicants' assertion, the prior art method necessarily includes *all* of the elements of the instant claims. That the determination of inherency in the instant case is not established by probabilities or possibilities is further evidenced by the teachings of Thompson *et al*. (*Diabetes* 46: Suppl. 1, page 30A, 0116, 02 May 1997, already of record) (Thompson *et al*. May, 1997). The reference of Thompson *et al*. is cited herein to solely rebut Applicants' arguments. Thompson *et al*. (May, 1997) showed that a method of subcutaneous administration of pramlintide, i.e., $^{25, 28, 29}$pro-h-amylin, an analog of human amylin, i.e., the same amylin agonist used in the instant invention, to patients with type II diabetes requiring insulin, at a dose 60 micrograms QID (i.e., four times a day) or TID (i.e., three times a day) not only improved glycemic control in these patients, ***but also decreased body weight*** (see abstract) concurrently. Therefore, the method of the '411 patent necessarily served as a method of treating obesity.

It is a commonly known fact in the art that type II diabetic patients (80-90% of whom are known to be obese) are 'in need of' obesity. Applicants themselves characterize Type 2 diabetic subjects taking insulin as a particularly difficult to treat obese subject population. See top of page 14 of Applicants after-final amendment. With regard to the Applicants' statement that Tsanev's disclosure that 80-90% of diabetic patients are obese falls short of the 100% (i.e., always, under any circumstances), the following must be noted. 'A generic claim cannot be allowed to an applicant if the prior art discloses a species falling within the claimed genus'. The species in that case will anticipate the genus. *In re Slayter*, 276 F.2d 408, 411, 125 USPQ 345, 347 (CCPA 1960); *In re Gosteli*, 872 F.2d 1008, 10 USPQ2d 1614 (Fed. Cir. 1989). A genus does not always anticipate a claim to a species within the genus. However, when the species is clearly named, the species claim is anticipated no matter how many other species are additionally named. In *In re Sivaramakrishnan*, 673 F.2d 1383, 213 USPQ 441 (CCPA 1982), the claims were directed to polycarbonate containing cadmium laurate as an additive. The court upheld the Board's

finding that a reference specifically naming cadmium laurate as an additive amongst a list of many suitable salts in polycarbonate resin anticipated the claims. The applicant had argued that cadmium laurate was only disclosed as representative of the salts and was expected to have the same properties as the other salts listed while, as shown in the application, *cadmium laurate had unexpected properties*. The court held that it *did not matter that the salt was not disclosed as being preferred*, *the reference still anticipated the claims* and because the claim was anticipated, *the unexpected properties were immaterial*. Although the instant claims are method claims, in the instant application, the prior art disclosure of a method comprising or consisting of the administration of 0.1 to 5 mg, or 0.5 to 1.0 mg of the amylin agonist, ^{25,28,29}Pro-human amylin alone or in conjunction with insulin or glucagon, to 80-90% of the human diabetic patients anticipates the instantly claimed method. The claims are anticipated because the administered ^{25,28,29}Pro-human amylin also inherently exerted obesity-relieving properties in said method. See also *Ex parte Novitski*, 26 USPQ2d 1389 (Bd. Pat. App. & Inter. 1993) (The Board rejected a claim directed to a method for protecting a plant from plant pathogenic nematodes by inoculating the plant with a nematode inhibiting strain of *P. cepacia*. A U.S. patent to Dart disclosed inoculation using *P. cepacia* type Wisconsin 526 bacteria for protecting the plant from fungal disease. Dart was silent as to nematode inhibition but the Board concluded that nematode inhibition was an inherent property of the bacteria. The Board noted that applicant had stated in the specification that Wisconsin 526 possesses an 18% nematode inhibition rating.). In the instant application, the obesity-relief or weight loss-induction is an intrinsic property inseparable from the administered pramlintide. The two structurally identical pramlintide compounds administered in the two methods (i.e., the prior art method and the instant method) cannot have mutually exclusive properties. As set forth above, this is evidenced by the teachings of Thompson *et al*. (*Diabetes* 46: Suppl. 1, page 30A, 0116, 02 May 1997, already of record) (Thompson *et al*. May, 1997). Thompson *et al*. (May, 1997) who showed that a method of subcutaneous administration of pramlintide, i.e., $^{25, 28, 29}$pro-h-amylin, an analog of human amylin, i.e., an amylin agonist, to patients with type II diabetes requiring insulin, at a dose 60 micrograms QID (i.e., four times a day) or TID (i.e., three times a day) not only improved glycaemic control in these patients, but also decreased body weight (see

abstract) concurrently, and therefore necessarily served as a method of treating obesity. The same two methods (i.e., the prior art method and the instant method) cannot have mutually exclusive results. The rejection stands.

In the instant application, it is important to note that the *human patients used in the instant specification for treatment of obesity via administration of pramlintide are indeed type II diabetic human patients*. Thus, the prior art disclosure is commensurate in scope with the instant disclosure with regard to the type 2 diabetic human subject population used, the pramlintide compound administered, the amount and frequency of pramlintide administered, to the type 2 diabetic human patients.

In the instant case, the claims are drawn to a method that uses generic human subjects. The method is not limited to treating obesity in non-diabetic obese human patients, but encompasses treating obesity in type II diabetic human patients, 80-90% of whom are known in the art to have intrinsic obesity. In other words, treatment of obesity in type II diabetic human patients is just one of the species or embodiments encompassed within the scope of the genus of human subjects in need of such treatment. That 10-20% of prior art diabetic patients, to whom pramlintide is administered, are not expected to be obese is not relevant since an anticipatory reference has to teach only one species or one embodiment encompassed by the scope of the genus claims. Under the principles of inherency, a reference may be directed to an entirely different problem than the one addressed by the inventor, or may be from an entirely different field of endeavor than that of the claimed invention, yet the reference is still anticipatory if it explicitly or inherently discloses every limitation recited in the claims. See *State Contracting & Eng'g Corp. v. Condotte America, Inc*., 346 F.3d 1057, 1068, 68 USPQ2d 1481, 1488 (Fed. Cir. 2003). Applicants appear to be arguing that in order to be anticipatory, a prior art reference has to teach each and every species or embodiment encompassed within the scope of the instant claims. The argument is not persuasive. The rejection stands.

12) The rejection of claims 7, 14 and 16 made in paragraph 27 of the Office Action mailed 02/11/08 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 11 and 13 of US patent 5,321,008 issued to Beumont *et al*. as evidenced by Tsanev (*Vutr. Boles* 23: 12-17, 1984, abstract, already of record) and

Rink *et al*. (US 5,739,106, already of record) ('106), is maintained for the reasons set forth therein and herein below.

Applicants submit almost the same arguments that they have presented on the obviousness double patenting rejection over US patent 5,686,411. Applicants are referred to the paragraph immediately above for the Office's response.

13) The rejection of claims 1, 7, 14 and 16 and the dependent claims 2-6, 9-13, 15 and 17 made in paragraph 28 of the Office Action mailed 02/11/08 under 35 U.S.C § 112, first paragraph, as containing new matter, is maintained for the reasons set forth therein and herein below.

Applicants point to lines 14 and 15 of page 9 of the specification wherein it is stated that '[t]reating or preventing obesity therefor includes the inhibition of weight gain and inducing weight loss in patients in need thereof' and assert that this sentence is supportive of the claim limitation 'an amount effective to inhibit weight gain or induce weight loss in said human subject'. With regard to the identified limitation of an amount of a composition 'comprising an amylin or an amylin agonist and a pharmaceutically acceptable carrier' being an amount effective to treat obesity which composition encompasses any other non-amylin or non-amylin agonist analogue elements such as insulin or glucagon etc., Applicants submit that the amount effective to treat obesity of 'a composition comprising the required amylin or amylin agonist of the invention' is determined by routine methods of pharmaceutical research, and that effectiveness is due to the amylin or amylin agonist, not any excipient.

Applicants' arguments have been carefully considered, but are not persuasive. The sentence '[t]reating or preventing obesity therefor includes the inhibition of weight gain and inducing weight loss in patients in need thereof' does not and cannot support 'an amount effective to inhibit weight gain or induce weight loss in said human subject'. The language 'composition comprising' similar to the limitations represents open-ended claim language and therefore, does not exclude additional, unrecited elements. See MPEP 2111.03 [R-1]. See *Moleculon Research Corp. v. CBS, Inc., 793 F.2d 1261, 229 USPQ 805 (Fed. Cir. 1986)*; *In re Baxter, 656 F.2d 679, 686, 210 USPQ 795, 803 (CCPA 1981)*; *Ex parte Davis, 80 USPQ 448, 450 (Bd. App. 1948)* ('comprising' leaves 'the claim open

for the inclusion of unspecified ingredients even in major amounts') [Emphasis added]. Therefore, the limitation 'comprising' in the instant claim(s) allows the inclusion of additional anti-obesity agents such as exendin, CCK etc., as well as elements such as insulin or glucagon, to be present in the recited composition. Therefore, an amount of a composition 'comprising' amylin or amylin agonist would include an amount of exendin, CCK, or insulin etc. There is no descriptive support for 'an amount of a composition comprising an amylin or amylin agonist' said 'amount effective to inhibit weight gain or weight loss' in said human subject. Instead, what is supported for example in Example 1 and Table I is an amount of the amylin agonist analogue pramlintide (e.g., 60 micrograms QID or TID) that is effective to decrease body weight.

With regard to the new matter rejection of claim 14, Applicants state that 'the concept of salts of the compounds of the invention' is found at lines 20-21 of page 20. Lines 20-21 from page 21 of the instant specification are reproduced below:

> the compounds referenced above may form salts with various inorganic and organic acids and bases. Such salts include salts prepared with organic and inorganic acids, for example,

These lines do not and cannot support the limitation in claim 14 of 'an amount of a salt of amylin or an amylin agonist compound' which is administered in a method of treating obesity in a human subject wherein said salt of amylin or an amylin agonist compound is administered in 'an amount effective to treat obesity in said subject by inhibiting weight gain or inducing weight loss' as claimed.

Applicants further submit that the term 'consisting' as used in claim 1 is a term of art (transitional claim language) that need not be specifically recited in the specification. However, the new matter rejection pertained to something more than the use of the term 'consisting' in claim 1. As set forth previously, claim 1 includes the limitation: 'method of treating obesity …. consisting of administering …. an amount effective to inhibit weight gain or induce weight loss …… of composition comprising an amylin or an amylin agonist and a pharmaceutically acceptable carrier'. A method of treatment of obesity 'consisting of' such an administration step *excludes,* for example, simultaneous insulin administration, or insulin administration minutes or hours before or after the administration. However, neither the original six claims, nor the description of the methods of treatment of the instant

invention support such a method of treating obesity 'consisting of' administering an effective …… composition comprising an amylin or an amylin agonist and a pharmaceutically acceptable carrier. For example, the originally filed specification at lines 6-8 of page 9 of the specification states [Emphasis added]:

> The present invention is directed to novel methods for treating or preventing obesity in humans *comprising* the administration of an amylin or an amylin agonist, the amylin agonist analogue ^{25,28,29}Pro-human amylin.

Pages 30-31 and Table I describe a statistically significant reduction in the mean baseline weight seen after the subcutaneous administration of 60 micrograms TID or 60 micrograms QID of one specific amylin agonist analogue species, pramlintide, to type II diabetic subjects for four weeks, wherein said pramlintide administration was accompanied *with the continued administration of insulin*. The method of treatment of obesity as described in the originally filed specification comprised insulin treatment *and* the administration of a specific dose of pramlintide to type II diabetic patients. This however does not provide descriptive support for the now claimed method of treating obesity in a human in need of treatment for obesity, said method 'consisting' of administering to said subject an amount of a composition as recited comprising an amylin or any amylin agonist and a pharmaceutically acceptable carrier, wherein said amount of the composition is effective to inhibit weight gain or induce weight loss in said subject. It is noted that Applicants have advanced no substantive arguments other than stating that the term 'consisting' in claim 1 is a term of the art that need not be specifically recited in the specification. The rejection stands.

14) The rejection of claims 1-7 and 9-17 made in paragraph 29 of the Office Action mailed 2/11/08 under 35 U.S.C § 112, first paragraph, as being non-enabling with regard to the scope, is maintained for the reasons set forth therein and herein below.

Applicants submit the following arguments:

(a) Applicants state that the proper standard for determining compliance with the enablement requirement is whether the specification provides sufficient information to permit one skilled in the art to make and use the claimed invention. *United States v. Telectronics, Inc.,* 8 USPQ2d 1217, 1223 (Fed. Cir. 1988). The test of enablement is not whether experimentation is necessary, but rather whether any experimentation that is necessary is

undue. A considerable amount of experimentation is permitted, provided that it is merely routine, or provided that the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *In re Wands,* 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). A specification that discloses how to make and use a claimed invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented "must be taken as in compliance with the enabling requirement of the first paragraph of $ 112 unless there is reason to doubt the objective truth of the statements contained therein." In *re Brana,* 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436, 1441 (Fed. Cir. 1995) (quoting In *re Marzocchi,* 439 F.2d 220, 223, 169 U.S.P.Q. 367, 369 (C.C.P.A. 1971) (emphasis in original)).

(b) With respect to reasons for doubting the objective truth of the specification, Applicants state that their comment in the Applicants' Appeal Brief filed July 2000 regarding the Rink patent is irrelevant. The Rink patent U.S. 5,739,106 only contemplates amylin-induced appetite suppression in rodents. Indeed, the Rink patent does not describe the treatment of obesity in humans using amylin or an amylin agonist as required by the claims of the present invention.

(c) Applicants cite *Wands* factors and state that it is well established that enablement does not require the inventor to submit an exact blueprint or recipe to practice the invention; thus, experimentation is allowed. *In re Angstadt,* 190 USPQ 214 (CCPA 1976). Regarding the quantity of experimentation needed, Applicants submit that the standard for determining enablement is whether the experimentation needed to practice the invention is undue or unreasonable. *Mineral Separation v. Hyde,* 242 U.S. 261,270 (1916). One of ordinary skill in the art would have the ability to select amylin and amylin agonist peptides for use in the claimed methods without undue experimentation in view of the specification.

(c) The specification *broadly* discloses that the claimed amylin compounds are useful in the treatment of obesity in a subject in need thereof. There is express guidance as to modes of administration, therapeutic dosages, mechanisms for assessing therapeutic efficacy, as well as a working example to demonstrate the statistically significant ability of an exemplary amylin compound to treat obesity in a human subject in need thereof. In the

working example, the human subjects were Type 2 diabetics. That the working example illustrated Type 2 diabetic subjects taking insulin does not render the scope of enablement limited to this subject population. Rather, it demonstrates that in a particularly difficult to treat, obese subject population (Type 2 diabetic subjects taking insulin), an exemplary amylin compound is therapeutically effective in the treatment of obesity. Taken together with the teachings of the specification (e.g., page 18, paragraph 3 to page 23, paragraph 2), the working example provides a base-line approach for establishing therapeutic efficacy of exemplary amylin compounds within the context of the presently claimed methods. Utilizing similar study structures, Applicants have in fact established that exemplary amylin compounds are effective in the treatment of obesity in non-diabetic subjects as well (see, e.g., IDS entries AZ1, AZ2, AZ4 and AZ5 of Aronne et *al.* and Smith et *al.* of record). This evidence confirms the teachings of Applicants specification, and demonstrates that Applicants' working example in fact provides enablement of the efficacy of a particularly difficult to treat, chronically obese subject population.

(d) The Office is attempting to limit the scope of enablement to the scope of Applicants' working examples. Based on the extensive guidance provided in the specification, including the human clinical study results, as well as the high level of skill in the art, the skilled artisan would be able to evaluate efficacy of amylin compounds in accordance with the methods of the inventions to ascertain therapeutically effective amounts of the recited amylin compounds. In fact, the Office's characterization of Example 1 only serves to underscore the enablement of the claims in this regard. Example 1 describes a clinical study wherein routine dosages were evaluated in human clinical subjects to ascertain a therapeutically effective dose as well as effective administration regimens.

(e) The relative skill of one skilled in the art to which the invention pertains is very high. In agreement with the Office's assertion, of the invention is pertinent to the treatment of obesity in a human subject in need of such treatment comprising or consisting of administering an amylin, an amylin agonist, or an amylin agonist analogue composition or compound in an amount effective to inhibit weight gain or induce weight loss in the subject. Specifically, the invention contemplates the treatment of obesity in human subject

in need of treatment by the administration of an amylin or amylin agonist. Applicants discovered that amylin or amylin agonists can be used for the treatment of obesity. The working examples, in combination with the disclosure of the specification and knowledge of one skilled in the art, amply enable the full scope of the invention as presently claimed. In agreement with the Office's assertion, obesity or adiposity as a 'chronic disease' that is highly prevalent in modem society and is strongly associated with multiple conditions including diabetes mellitus, insulin resistance, hypertension, etc. One of ordinary skill in the art would have the ability to select amylin and amylin agonist peptides for use in the claimed methods without undue experimentation. Indeed, amylin compounds recited in the claims are generally recognized as a defined class of compounds, and the specification provides ample direction and guidance to those skilled in the art with regard to the identification of such amylin compounds useful in the context of the claimed methods.

(f) With regard to unpredictability, the Office asserts that both Baron *et al.* and Ratner *et al.* indicate the impracticability of using amylin as a therapeutic agent. Whether native human amylin is suitable for use as a commercial drug product is not a proper standard for judging the enablement of the present claims. Moreover, contrary to the Examiner's characterization of the cited references, it is submitted that both Baron *et al.* and Ratner *et al.* actually support enablement of the claimed invention. That is, given the teachings of the instant specification, one of ordinary in the art would have the ability to select amylin and amylin agonist peptides for use in the claimed methods without undue experimentation. This further confirms that both amylin and amylin agonists are well known compounds that have been widely characterized. Given this, one of ordinary skill in the art would have the requisite skill to practice the invention commensurate in scope with the claims without undue experimentation.

(g) With regard to the breadth of the claims, the Office impermissibly attempts to limit the invention to the scope of the examples. As set forth in MPEP 2164.02, '[f]or a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art (in view of level of skill, state of the art and the information in the specification) would expect the claimed genus could be used in that manner without undue experimentation.' This is exactly what Applicants have

provided. For example, Tables I - I1 and Examples 1-8 disclose data relating to the claimed methods and exemplary amylin compounds. Alone, this disclosure is sufficient such that one of ordinary skill in the art at the time the invention was made would have the ability to practice the invention commensurate in scope with the claims. With regard to the Office's statement that "the only amylin agonist analogue species within the recited broad genus that is being used for inducing weight loss in humans is pramlintide", Applicants state that the Office appears to be focusing on Example 1 rather than the teachings of the specification as a whole and the level of ordinary skill in the art.

(h) Amylin compounds recited in the claims are generally recognized as a defined class of compounds, and the specification provides ample direction and guidance to those skilled in the art with regard to the identification of such amylin compounds useful in the context of the claimed methods. The specification is replete with examples of amylin agonists, including functional variants, fragments, and derivatives of amylin and amylin agonists. For example, given at least the discussion in the background concerning amylin agonists, as well as the description of SEQ ID NO: 12-17, one of ordinary skill in the art having read the specification would have the ability to select known amylin agonists without undue experimentation. Moreover, to the extent that any additional experimentation may be required, Applicants note that the performance of routine and well known steps cannot create undue experimentation even if it is laborious. See *In re Wands* (Id.); *In re Angstadt (Id.)*.

(i) Given the knowledge in the art, and based on the guidance provided in the specification regarding the extensive exemplary embodiments of amylin compounds, receptor binding assays and other assays for determining amylin activity, including the soleus muscle assay, and exemplary clinical study designs, additional therapeutically active amylin agonists can be identified within the context of the present claims without the need for undue experimentation. Based on such guidance, one of skill in the art would be able to practice the claimed invention with only routine experimentation. Certain of the dependent claims recite specific types of amylin compounds (e.g., amylin agonist analogues including the amylin agonist analogue of SEQ ID NO: 1). As generally uderstood by those of skill in

the art, amylin analogues are compounds that are structurally related to the reference compound, i.e., amylin. As explained in the specification and understood by those skilled in the art, an amylin analogue can have one or more amino acid substitutions, deletions, inversions, or additions compared to a native or naturally occurring amylin. Furthermore, the claims clarify that the amylin analogue is an amylin agonist analogue. Thus, in accordance with the claims and the knowledge of those of ordinary skill in the art, the recited amylin agonist analogues are both structurally and functionally defined.

Applicants' arguments have been carefully considered, but are not persuasive. Contrary to Applicants' assertion, representative examples of amylin agonists or amylin agonist analogues of the claimed genus together with a statement applicable to the genus as a whole is not sufficient to enable the full scope of the claimed invention, because one skilled in the art would not expect that the claimed genus could be used in that manner without undue experimentation. For example, at the time of the invention, amylin at a dose varying from about 0.1 to 10 mg (which dose encompasses the doses recited in the instant claims, including claims 6 and 9-13) was administered to treat patients suffering from *anorexia or patients deficient in adipose tissue*. See claims and page 13 of Rink *et al*. (WO 9220367, already of record) which is cited herein solely to rebut Applicants' arguments. Applicants have readily acknowledged previously that administration of amylin would have lead to *weight gain* rather than *weight decrease* as was known at the time of the invention via the disclosure of US patents 5,364,841 and 5,280,014 (both of record). Applicants have expressly stated previously that at the time of the invention, amylin was administered to patients suffering from *anorexia* or *a similar condition* 'in order to increase weight'. See pages 7 and 8 of Applicants' amendment filed 03/22/99. This alone is *prima facie* evidence for the lack of enablement of the instantly claimed method of treating obesity by administration of amylin as claimed. Therefore, despite the level of skill in the art and despite the structural relatedness to pramlintide, there is no predictability that administration of a dose of amylin varying from about 0.1 to 10 mg to a human patient would have resulted in inhibition of weight gain or induction of weight loss. Instead, one of skill in the art would have expected induction of weight gain as acknowledged by Applicants. Thus, there are reasons for doubting the objective truth of the specification.

With the weight gain-increasing effect of amylin known at the time of the invention, one of skill in the art would have reasonably expected amylin and the innumerable number of non-pramlintide amylin agonists or amylin agonist analogues encompassed within the scope of the instant claims, to be therapeutic against anorexia. Therefore, the administration of amylin or a non-pramlintide amylin agonist analogue would not have predictably brought about weight gain inhibiting or weight loss inducing effect. Therefore, contrary to Applicants' assertion, the considerable amount of experimentation needed in the instant case is not merely routine, but undue in view of the unpredictability and the lack of evidence enabling the full scope of the invention. Except for pramlintide, Applicants have not established that a representative number of the vast number of exemplary amylin compounds encompassed within the scope of the claims is indeed effective in the treatment of obesity in diabetic or non-diabetic subjects. Even if a skilled artisan selected some of the exemplary amylin agonist analogues recited in the instant specification, there is no predictability that said non-pramlintide amylin agonist analogues would have the therapeutic effect against a particularly difficult to treat obese diabetic or morbidly obese human subjects and is usable in the claimed method. The rejection stands.

With regard to Applicants' arguments on the reasons for doubting the objective truth of the specification and Applicants' comments on the limitation 'an amount effective to treat obesity' particularly in connection with amylin, a nonpramlintide amylin agonist, a non-pramlintide amylin agonist analogue, a salt of amylin, and a salt of amylin agonist, the following should be noted. The post-filing references of Aronne et *al.* and Smith et *al.* do not show that administration of amylin or a non-pramlintide amylin agonist analogue as claimed in the instant claims results in inhibition of weight gain or induction of weight loss in diabetic or non-diabetic human subjects in need of treatment of obesity. As set forth above, at the time of the invention, amylin at a dose varying from about 0.1 to 10 mg was administered to treat patients suffering from anorexia or patients deficient in adipose tissue. See claims and page 13 of Rink *et al*. WO 9220367. Note that the instantly recited 30 to 300 micrograms per dose of amylin falls within Rink's anorexia-treating dose. Therefore, there was no predictability that administration of a dose varying from about 0.1 to 10 mg of amylin to a human patient would have resulted in inhibition of weight gain or induction of

weight loss. Instead of weight loss, one of skill in the art would have expected induction of weight gain. This is yet another reason for doubting the objective truth of the specification. In view of this, Applicants' description of exemplary amylin agonist compounds alone is insufficient to enable the full scope of the claimed invention. Thus, given this knowledge in the art of the therapeutic effect of amylin against anorexia despite its amylin agonistic characteristics as measured by receptor binding assays and the soleus muscle assay etc., the breadth of the claims, the lack of predictability when viewed in combination with Rink's ('367) showing that the administration of about 0.1 to 10 mg amylin is therapeutic against anorexia, Applicants' own previous acknowledgment that administration of amylin would have lead to *weight gain* rather than *weight decrease* as was known at the time of the invention, and the lack of working examples enabling the full scope of the claimed invention, one of skill in the art would have required considerable amount of undue experimentation to practice the full scope of the instant invention. The rejection stands.

15) The rejection of claims 1-7, 9-14, 16 and 17 made in paragraph 33 of the Office Action mailed 02/11/08 under 35 U.S.C § 102(a) as being anticipated by Kolterman *et al*. (WO 96/40220, already of record) as evidenced by Tsanev (*Vutr. Boles* 23: 12-17, 1984, abstract, already of record), is maintained for the reasons set forth therein and herein below.

Applicants submit the following arguments:

(a) Applicants cite case law, MPEP § 2131 and state that in order to anticipate a claim, a single prior art reference must provide each and every element set forth in the claim. (b) Kolterman '220 describes the use of an amylin agonist (i.e., pramlintide) for treating type II diabetes mellitus. Kolterman '220 merely demonstrates that administration of an amylin agonist significantly reduces postprandial plasma glucose concentrations in patients with type II diabetes mellitus. (c) Kolterman '220 does not teach the use of an amylin or amylin agonist for treating obesity or demonstrate a reduction in body weight in those patients administered an amylin or amylin agonist. (d) Kolterman '220 is silent with regard to the effect of an amylin or an amylin agonist on body weight. Whether or not Kolterman '220 discloses that weight loss is beneficial is irrelevant. (e) Tsanev's disclosure that 80-90% of diabetic patients are obese falls short of the 100% (i.e., always, under any

circumstances) criterion required by the present claims and required by the law. (f) Kolterman '220 does not provide each and every element of the claimed invention.

Applicants' arguments have been carefully considered, but are not persuasive. Contrary to Applicants' assertion, the prior art method necessarily includes *all* of the elements of the instant claims. As set forth previously, Kolterman *et al*. ('220) taught a method of administering to an insulin-taking type II diabetic human subject a dose of 10, 30, 50, 60 or 150 micrograms per day (i.e., the amount falling in the range recited in the instant claims) of the amylin agonist composition, pramlintide or $^{25, 28, 29}$pro-h-amylin, also known as AC137 (i.e., SEQ ID NO: 1), i.e., the same amylin agonist administered in the instantly claimed method. The composition consists of pramlintide and a pharmaceutically acceptable carrier, and is administered in single or multiple doses, for example, of about 30 micrograms QID, or about 60 micrograms TID or QID, i.e., an amount effective to inhibit weight gain or induce weight loss. See pages 9-11; paragraph bridging pages 20 and 21; page 21; first paragraph on page 19; lines 8-10 on page 19; and the first row reciting 'Insulin-Treated Patients' in each Table of Kolterman *et al*. ('220). Pramlintide is administered subcutaneously 1-4 times a day, before meals. See pages 9 and 22. Kolterman *et al*. ('220) additionally taught that the presence of obesity is a characteristic of 'most patients with Type II diabetes mellitus' (i.e., in need of treatment of obesity). See page 10. Kolterman *et al*. ('220) taught the benefit of obtaining weight loss in Type II diabetic patients by teaching that hyperglycemia associated with Type II diabetes can be reversed or ameliorated by *weight loss* sufficient to restore the sensitivity of the peripheral tissues to insulin (see pages 7, first paragraph), thus teaching that Type II diabetic patients are in need of weight loss or treatment of obesity. Thus, the very active step of the instantly claimed method was disclosed and practiced by Kolterman *et al*. ('220) in 1996 in the very same patient, i.e., a human type II diabetes mellitus patient used by Applicants in Example 1 of the instant application. The prior art method is the *same* as the instantly claimed method in terms of the pramlintide amylin agonist or the amylin agonist analogue, the pramlintide amylin agonist composition, or the pramlintide amylin agonist analogue composition administered, and the insulin-taking Type II diabetic patient used (80-90% of Type II diabetic patients being known in the art to be intrinsically obese as taught by Tsanev - see

Tsanev's abstract), the subcutaneous route of administration used, the dose and the daily frequency of the amylin agonist pramlintide administered, and the administration step prior to meals. Given Tsanev's express disclosure that 80 to 90% of type II diabetic patients are intrinsically obese, and given Kolterman's ('220) recognition that obesity is an intrinsic characteristic of most patients with Type II diabetes mellitus and the indication that these patients are in need of weight loss, Kolterman's ('220) method of subcutaneous administration of pramlintide to Type II diabetic patients in an amount that falls within the range recited in the instant claims, necessarily serves as the claimed method of treating obesity and therefore anticipates the instantly claimed method. 80-90% of Type II diabetic patients Kolterman's ('220) type II diabetic obese patients to whom pramlintide composition is administered necessarily qualify as human subjects in need of treatment of obesity as recited in the instant claims. Since the structural limitations of the instantly claimed method and *all* of the criteria required by the instant claims are met by the teachings of Kolterman *et al*. ('220), Kolterman's ('220) method is expected to serve necessarily as the instantly claimed method and is expected to bring about the obesity-treating effect, weight gain inhibiting effect, or weight loss-inducing effect. The Office's position that Kolterman's ('220) method is the same as the Applicants' claimed method is based upon the fact that the method step, the pramlintide compound administered, the amount of the compound administered, the route by which the compound is administered, and the intrinsically obese diabetic human patient species to which the pramlintide compound is administered, are the *same* in the two methods. The art-recognized intrinsic obesity being prevalent in 80 to 90% of diabetic patients as disclosed by Tsanev (see abstract), Kolterman's ('220) method of administration of the above-identified therapeutically effective amount (i.e., about 30 micrograms QID, or about 60 micrograms TID or QID, or a dose of 10, 30, 50, 60 or 150 micrograms per day) of the amylin agonist ^{25,28,29}Pro-human amylin to intrinsically obese type 2 diabetic human subject species anticipates the instant claims. That 10-20% of Kolterman's ('220) diabetic patients, also to whom pramlintide is administered, are not expected to be obese is not relevant since an anticipatory reference does not have teach every species or every embodiment encompassed by the scope of the claims. Given that the method step of the Kolterman's ('220) method and the instant claims

are the same, Kolterman's ('220) method is expected to bring about weight gain-inhibiting or weight loss-causing therapeutic effect in the intrinsically obese pramlintide-treated type II diabetic patient. Contrary to Applicants' assertion, the prior art method necessarily includes *all* of the elements of the instant claims. That the determination of inherency in the instant case is not established by probabilities or possibilities is further evidenced by the teachings of Thompson *et al*. (*Diabetes* 46: Suppl. 1, page 30A, 0116, 02 May 1997, already of record) (Thompson *et al*. May, 1997). Thompson *et al*. (May, 1997) who showed that a method of subcutaneous administration of pramlintide, i.e., $^{25, 28, 29}$pro-h-amylin, an analog of human amylin, i.e., an amylin agonist, to patients with type II diabetes requiring insulin, at a dose 60 micrograms QID (i.e., four times a day) or TID (i.e., three times a day) not only improved glycemic control in these patients, but ***also decreased body weight*** (see abstract) concurrently, and therefore necessarily served as a method of treating obesity. Since the prior art clearly teaches the instantly claimed method, any assertions of specific functional properties attributed to the amylin agonist pramlintide administered in the claimed method are merely inherent and do not necessarily make the claimed method patentable. *Ex parte Novitski*, 26 USPQ2d 1389 (Bd. Pat. App. & Inter. 1993) (The Board rejected a claim directed to a method for protecting a plant from plant pathogenic nematodes by inoculating the plant with a nematode inhibiting strain of *P. cepacia*. A U.S. patent to Dart disclosed inoculation using *P. cepacia* type Wisconsin 526 bacteria for protecting the plant from fungal disease. Dart was silent as to nematode inhibition but the Board concluded that nematode inhibition was an inherent property of the bacteria. The Board noted that applicant had stated in the specification that Wisconsin 526 possesses an 18% nematode inhibition rating.). In the instant application, the obesity-relief or weight loss-induction is an inherent property inseparable from the administered pramlintide. Since the structural limitations of the instantly claimed method and *all* of the criteria required by the instant claims are met by the disclosure of Kolterman *et al*. ('220), Kolterman's ('220) method is expected to serve necessarily as the instantly claimed method and is expected to bring about the weight gain inhibiting effect, weight loss-inducing effect, or obesity-treating effect. The two structurally identical pramlintide compounds administered in the two methods (i.e., the prior art method

and the instant method) cannot have mutually exclusive properties. The same two methods cannot have mutually exclusive results.

It is a commonly known fact in the art that type II diabetic patients (80-90% of whom are known to be obese) are 'in need of' obesity. Applicants themselves characterize Type 2 diabetic subjects taking insulin as a particularly difficult to treat obese subject population. See top of page 14 of Applicants after-final amendment. With regard to the Applicants' statement that Tsanev's disclosure that 80-90% of diabetic patients are obese falls short of the 100% (i.e., always, under any circumstances), the following must be noted. 'A generic claim cannot be allowed to an applicant if the prior art discloses a species falling within the claimed genus'. The species in that case will anticipate the genus. *In re Slayter*, 276 F.2d 408, 411, 125 USPQ 345, 347 (CCPA 1960); *In re Gosteli*, 872 F.2d 1008, 10 USPQ2d 1614 (Fed. Cir. 1989). A genus does not always anticipate a claim to a species within the genus. However, when the species is clearly named, the species claim is anticipated no matter how many other species are additionally named. In *In re Sivaramakrishnan*, 673 F.2d 1383, 213 USPQ 441 (CCPA 1982), the claims were directed to polycarbonate containing cadmium laurate as an additive. The court upheld the Board's finding that a reference specifically naming cadmium laurate as an additive amongst a list of many suitable salts in polycarbonate resin anticipated the claims. The applicant had argued that cadmium laurate was only disclosed as representative of the salts and was expected to have the same properties as the other salts listed while, as shown in the application, *cadmium laurate had unexpected properties*. The court held that it *did not matter that the salt was not disclosed as being preferred*, *the reference still anticipated the claims* and because the claim was anticipated, *the unexpected properties were immaterial*. Although the instant claims are method claims, in the instant application, the prior art disclosure of a method comprising or consisting of the administration of 30 or micrograms of the amylin agonist, ^{25,28,29}Pro-human amylin, to 80-90% of the human diabetic patients anticipates the instantly claimed method. The claims are anticipated because the administered ^{25,28,29}Pro-human amylin also inherently exerted obesity-relieving properties in said method. See also *Ex parte Novitski*, 26 USPQ2d 1389 (Bd. Pat. App. & Inter. 1993) (The Board rejected a claim directed to a method for protecting a plant from plant pathogenic nematodes by

inoculating the plant with a nematode inhibiting strain of *P. cepacia*. A U.S. patent to Dart disclosed inoculation using *P. cepacia* type Wisconsin 526 bacteria for protecting the plant from fungal disease. Dart was silent as to nematode inhibition but the Board concluded that nematode inhibition was an inherent property of the bacteria. The Board noted that applicant had stated in the specification that Wisconsin 526 possesses an 18% nematode inhibition rating.). In the instant application, the obesity-relief or weight loss-induction is an intrinsic property inseparable from the administered pramlintide. The two structurally identical pramlintide compounds administered in the two methods (i.e., the prior art method and the instant method) cannot have mutually exclusive properties. As set forth above, this is evidenced by the teachings of Thompson *et al*. (*Diabetes* 46: Suppl. 1, page 30A, 0116, 02 May 1997, already of record) (Thompson *et al*. May, 1997).

In the instant application, it is important to note that the *human patients used in the instant specification for treatment of obesity via administration of pramlintide are indeed type II diabetic human patients*. Thus, the prior art disclosure is commensurate in scope with the instant disclosure with regard to the type 2 diabetic human subject population used, the pramlintide compound administered, the amount and frequency of pramlintide administered, to the type 2 diabetic human patients.

In the instant case, the claims are drawn to a method that uses generic human subjects. The method is not limited to treating obesity in non-diabetic obese human patients, but encompasses treating obesity in type II diabetic human patients, 80-90% of whom are known in the art to have intrinsic obesity. In other words, treatment of obesity in type II diabetic human patients is just one of the species or embodiments encompassed within the scope of the genus of human subjects in need of such treatment. That 10-20% of prior art diabetic patients, to whom pramlintide is administered, are not expected to be obese is not relevant since an anticipatory reference has to teach only one species or one embodiment encompassed by the scope of the genus claims. Under the principles of inherency, a reference may be directed to an entirely different problem than the one addressed by the inventor, or may be from an entirely different field of endeavor than that of the claimed invention, yet the reference is still anticipatory if it explicitly or inherently discloses every limitation recited in the claims. See *State Contracting & Eng'g Corp. v.*

Condotte America, Inc., 346 F.3d 1057, 1068, 68 USPQ2d 1481, 1488 (Fed. Cir. 2003). Applicants appear to be arguing that in order to be anticipatory, a prior art reference has to teach each and every species or embodiment encompassed within the scope of the claims. The argument is not persuasive.

Claims 1-7, 9-14, 16 and 17 are anticipated by Kolterman *et al*. ('220). The publication of Tsanev is **not** used as a secondary reference in combination with the reference of Kolterman *et al*. ('220), but rather is used to show that every element of the claimed subject matter is disclosed by Kolterman *et al*. ('220), with the unrecited limitation(s) being inherent as evidenced by the state of the art. See *In re Samour* 197 USPQ 1 (CCPA 1978). 'To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill.' *Continental Can Co. USA v. Monsanto Co*., 948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991). Note that as long as there is evidence of record establishing inherency, failure of those skilled in the art to contemporaneously recognize an inherent property, function or ingredient of a prior art reference does not preclude a finding of anticipation. *Atlas Powder Co. v. IRECO Inc*., 190 F.3d 1342, 1349, 51 USPQ2d 1943, 1948 (Fed. Cir. 1999). See MPEP 2124. The alleged failure of Kolterman ('220) to expressly mention treatment of obesity as a goal is irrelevant. To the extent the method embodiment in the claimed invention achieves treatment of obesity, so does the method of Kolterman's ('220). Where the result is a necessary consequence of what was deliberately intended, it is of no import that the article's authors did not appreciate the results. See *Mehl/Biophile International Corp. v. Milgraum*, U.S. Court of Appeals Federal Court, 52 USPQ2d 1303 and 1306, 192 F3d 1362, 1999 citing *W.L. Gore & Assocs. v. Garlack, Inc*., 721 F.2d 1540, 1548, 220 USPQ 303, 309 (Fed. Cir. 1983). The rejection stands.

16) The rejection of claims 7, 14 and 16 made in paragraph 34 of the Office Action mailed 02/11/08 under 35 U.S.C § 102(e)(2) as being anticipated by Beumont *et al*. (US

5,321,008, already of record) ('008) as evidenced by Tsanev (*Vutr. Boles* 23: 12-17, 1984, abstract, already of record), is maintained for the reasons set forth therein and herein below.

Applicants submit almost the same arguments that they have presented on the obviousness double patenting rejection over US patent 5,321,008. Applicants are referred to paragraph 12 above for the Office's response.

17) The rejection of claims 7, 14, 16 and 17 made in paragraph 35 of the Office Action mailed 02/11/08 under 35 U.S.C § 102(e)(2) as being anticipated by Gaeta *et al*. (US 5,686,411, already of record) ('411) as evidenced by Tsanev (*Vutr. Boles* 23: 12-17, 1984, abstract, already of record), is maintained for the reasons set forth therein and herein below.

Applicants submit almost the same arguments that they have presented on the obviousness double patenting rejection over US patent 5,686,411. Applicants are referred to paragraph 11 above for the Office's response.

18) The rejection of claims 1-7, 9, 11-14, 16 and 17 made in paragraph 36 of the Office Action mailed 02/11/08 under 35 U.S.C § 102(b) as being anticipated by Kolterman *et al*. (*Diabetologia* 39: 492-499, April, 1996, already of record) (Kolterman *et al*., 1996) as evidenced by Itasaka *et al*. (*Psychiatr. Clin. Neurosci.* 54: 340-341, June 2000, already of record), is maintained for the reasons set forth therein and herein below.

Applicants submit the following arguments:

(a) Applicants state that Kolterman 1996 merely describes the use of an amylin agonist, pramlintide, for treating patients with insulin-dependent diabetes mellitus and demonstrates that administration of the amylin agonist significantly reduces postprandial plasma glucose concentrations. (c) Kolterman 1996 does not teach the use of an amylin agonist for treating obesity or demonstrate a reduction in body weight in those patients administered the amylin agonist. (d) Kolterman 1996 does not report the weight of the subjects at the end of the study and nothing in the reference indicates that pramlintide had any effect on the weight of the subjects. (e) Kolterman 1996 is silent with regard to the effect of an amylin or an amylin agonist on body weight. (e) The patient population of Kolterman 1996 is not necessarily the same as the claimed subject, i.e., a subject in need of treatment for obesity. (f) Applicants cite case law and state that the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the

inherency of that result or characteristic. To establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the references, and that it would be so recognized by persons of ordinary skill. (g) Inherency may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. (f) The phrase 'in need thereof' is meaningful and gives life and meaning to the preambles' statement of purpose. (g) Kolterman 1996 does not provide each and every element of the claimed invention.

Applicants' arguments have been carefully considered, but are not persuasive. Contrary to Applicants' assertion, the prior art method necessarily includes *all* of the elements of the instant claims. As set forth previously, Kolterman *et al*. (1996) taught a method of subcutaneous administration of 30, 100, or 300 μg of pramlintide composition or AC137 (i.e., $^{25, 28, 29}$pro-h-amylin), a human amylin analogue, to human patients with insulin-dependent diabetes mellitus or IDDM who are on insulin. Pramlintide is administered three times daily for a period of 14 days. See abstract; and page 493. The mean body weight $\pm$ SEM of diabetic patients included in Kolterman's (1996) method who were administered subcutaneously with 30 micrograms, 100 micrograms, and 300 micrograms of pramlintide, three times a day for 14 days, was 70.6 $\pm$ 2.7, 74.4 $\pm$ 2.5, and 75.7 $\pm$ 2.6 respectively, a body weight similar to the 70 kg body weight of the human patient disclosed at lines 4-8 of page 23 of the substitute specification; and paragraph bridging pages 23 and 24 and lines 3-7 on page 24 of Applicants' response filed December 2002. Note that the human patient in need of the recited treatment according to the instant invention is expressly identified in the instant specification as one having a body weight of 79 kg. For example, the recited therapeutic amount range of 'about 0.1 milligrams per day to about 1 milligram per day', or 'about 0.01 to about 5 mg/day', or 0.03 to about 5 mg/day of the amylin agonist or amylin agonist analogue, pramlintide, administered is specifically "for a 70 kg patient". See lines 4-8 of page 23 of the substitute specification; and paragraph bridging pages 23 and 24 and lines 3-7 on page 24 of Applicants' response filed December 2002. Therefore, the 70.6 to 75.7 kg diabetic patients from Kolterman's (1996) study qualify as 'human subjects in need thereof' as recited in the instant claims. Additionally,

even BMI-wise, Kolterman's (1996) diabetic subjects meet the limitation 'human subjects in need thereof' as recited in the instant claims, because the diabetic subjects included in Kolterman's method (1996) had a BMI of up to 27 (see second full paragraph under 'Subjects, materials and methods). Therefore, Kolterman's (1996) diabetic subjects having a BMI at least in the range of 24 up to 27 do qualify as obese diabetic subjects in light of what is known in the art. For example, Itasaka *et al*. teach that a BMI of 24.0 to 26.4 represents mild obesity and 26.4 and heavier (i.e., including a BMI of 26.4 to 27) represents obesity in humans (see abstract of Itasaka *et al*.). Kolterman's (1996) pramlintide composition did not comprise another obesity relief agent, but consisted of or consisted essentially of pramlintide. The pramlintide composition was injected subcutaneously to the human patients (see 'Study design') and therefore is expected to inherently contain a pharmaceutically acceptable carrier therein. The amount administered was 30 micrograms three times a day to 'about 0.1 milligrams' or 300 micrograms per day. See 'Study design'; Table 1; and paragraph there below. Kolterman's (1996) subcutaneous administration of a therapeutically effective amount of the amylin agonist ^{25,28,29}Pro-human amylin to diabetic human subjects weighing 70 kg or more, or having a BMI falling in the BMI range of 24 up to 27 anticipates the instant claims. Thus, the very active step recited in the instantly claimed method was disclosed and practiced by Kolterman *et al*. in April, 1996. The prior art method of administering the above-explained amount of the amylin agonist ^{25,28,29}Pro-human amylin (pramlintide or SEQ ID NO: 1) to diabetic human subjects weighing 70 kg or more, and/or having a BMI falling in the range of 24 up to 27 necessarily serves as the Applicants' method. Given that the method step in Kolterman's (1996) method and the instant claims are the *same* and the amount administered are the *same*, Kolterman's (1996) method is expected to necessarily bring about the same therapeutic effect in the pramlintide-treated diabetic patients as defined in the instant invention, i.e., by controlling body weight for cosmetic purposes, or by improving bodily appearance in the diabetic patients. That the determination of inherency in the instant case is not established by probabilities or possibilities is further evidenced by the teachings of Rattner *et al*. (*Exp. Clin. Endocrinol. Diabetes* 113: 199-204, 2005). The reference of Rattner *et al*. is set forth herein solely to address Applicants' arguments. The reference of Rattner *et al*., which is co-authored by OG

Kolterman, show that subcutaneous administration of 30 or 60 micrograms of TID or QID pramlintide to insulin-taking IDDM patients having a body weight of 76.0 ± 14.3 kg or a BMI of > 25 kg/m^2, concurrently induced *a significant decline in weight* (see sections 'Subjects and Methods'; Results; Table 1; and Figure 1B) and therefore necessarily served as a method of treating obesity. Since the prior art clearly teaches the instantly claimed method, any assertions of specific functional properties attributed to the amylin agonist pramlintide administered in the claimed method are merely inherent and do not necessarily make the claimed method patentable. *Ex parte Novitski*, 26 USPQ2d 1389 (Bd. Pat. App. & Inter. 1993) (The Board rejected a claim directed to a method for protecting a plant from plant pathogenic nematodes by inoculating the plant with a nematode inhibiting strain of *P. cepacia*. A U.S. patent to Dart disclosed inoculation using *P. cepacia* type Wisconsin 526 bacteria for protecting the plant from fungal disease. Dart was silent as to nematode inhibition but the Board concluded that nematode inhibition was an inherent property of the bacteria. The Board noted that applicant had stated in the specification that Wisconsin 526 possesses an 18% nematode inhibition rating.). In the instant application, the obesity-relief or weight loss-induction is an inherent property inseparable from the administered pramlintide. Since the structural limitations of the instantly claimed method and *all* of the criteria required by the instant claims are met by the disclosure of Kolterman *et al*. ('1996), Kolterman's ('1996) method is expected to serve necessarily as the instantly claimed method and is expected to bring about the weight gain inhibiting effect, weight loss-inducing effect, or obesity-treating effect. The two structurally identical pramlintide compounds administered in the two methods (i.e., the prior art method and the instant method) cannot have mutually exclusive properties. The same two methods cannot have mutually exclusive results. The rejection stands.

Relevant Art

19) The art made of record and not currently relied upon in any of the rejections is considered pertinent to Applicants' disclosure:

The 'Editorial' by Pi-Sunyer *et al.* (*Diabetes Care* 28: 1526-1527, 2005) teach that a guiding principle in the treatment of type 2 diabetic patients has been the recommendation to lose weight (1, 2). See the first paragraph of the 'Editorial'.

Remarks

20) Claims 1-7 and 9-17 stand rejected.

21) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. The Fax number for submission of amendments, responses and/or papers is (571) 273-8300, which receives transmissions 24 hours a day and 7 days a week.

22) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.Mov. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (in USA or CANADA) or 571-272-1000.

23) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's Supervisor, Shanon Foley, can be reached on (571) 272-0898.

/S. Devi/
S. Devi, Ph.D.
Primary Examiner
AU 1645

April, 2008